DOI:10.3724/cbls.2026028 **CSTR**:32203.14.cbls.2026028
文章编号:1004-0374(2026)03-0503-14

组蛋白赖氨酸去甲基化酶5A在肿瘤中的研究进展

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摘 要:组蛋白赖氨酸去甲基化酶(KDM)5A可以通过催化组蛋白赖氨酸残基去甲基化调控基因转录,在细胞增殖及分化等过程中发挥重要调控作用。近年来研究发现,KDM5A在多种肿瘤中异常表达,通过多种信号通路及相关分子机制来调控肿瘤的发生及进展。同时,KDM5A与肿瘤患者的耐药和预后密切相关,是潜在的预后预测标志物和治疗靶点。本文对KDM5A的结构、生物学功能、在肿瘤进展和耐药中的作用机制和靶向KDM5A抗肿瘤药物的应用进展作一综述,为恶性肿瘤的精准治疗提供一定的思路。

关键词:组蛋白赖氨酸去甲基化酶(KDM) 5A;肿瘤;肿瘤增殖;肿瘤免疫治疗
中图分类号:Q55;R730 **文献标识码**:A

Research progress of histone lysine demethylase 5A in tumors

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Abstract: Histone lysine demethylase (KDM) 5A can specifically remove the dimethyl and trimethyl groups on histone H3 lysine 4 (H3K4me2/3). This activity enables KDM5A to modulate chromatin structure and gene transcription, thereby influencing fundamental cellular processes such as proliferation, differentiation, and apoptosis. Notably, KDM5A is frequently dysregulated across a wide spectrum of malignancies. This review aims to provide a comprehensive and updated synthesis of the multifaceted roles of KDM5A in tumor biology, encompassing its molecular mechanisms in cancer progression, its contribution to therapy resistance, its complex interplay with tumor immunotherapy, and the current landscape of targeted pharmacological inhibition. The core content of this review systematically dissects the oncogenic functions of KDM5A. Structurally, KDM5A possesses multiple functional domains that facilitate chromatin recruitment and enzymatic activity. Biologically, it exerts context-dependent dual roles in regulating cell cycle and differentiation, often promoting tumorigenesis by silencing tumor suppressors. The molecular mechanisms driving cancer progression are elaborated across several key pathways. KDM5A promotes tumor proliferation and migration by modulating the PI3K/AKT signaling axis through targeting regulators like ROCK1/PTEN and FXYD3. It facilitates epithelial-mesenchymal transition (EMT), a critical step in metastasis, by repressing epithelial markers and activating mesenchymal markers. Furthermore, KDM5A enhances tumor cell survival by downregulating pro-apoptotic genes and cell cycle inhibitors. Its role extends to suppressing anti-tumor immunity by downregulating antigen-presentation genes. A particularly significant section addresses KDM5A′s central role in fostering drug tolerance and resistance to chemotherapeutic agents and targeted therapies, often through epigenetic silencing of key sensitivity genes. Paradoxically, emerging evidence also implicates KDM5A in potentiating response to immune checkpoint blockade (ICB) therapy. By repressing PTEN, KDM5A can activate the PI3K-AKT-S6K1 pathway, leading to upregulated PD-L1 expression and enhanced recruitment of $CD8^+$ T cells, suggesting a complex, context-dependent interaction with the tumor immune microenvironment. Given its prominent oncogenic functions, KDM5A has emerged as a

收稿日期:2025-06-12; **修回日期**:2025-07-30
基金项目:国家自然科学基金项目(81770165)
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compelling therapeutic target. We review the development and preclinical application of various KDM5A inhibitors. These compounds have shown efficacy in inhibiting tumor growth, overcoming drug resistance, and synergizing with existing therapies in model systems. In conclusion, KDM5A is a master epigenetic regulator deeply involved in tumor initiation, progression, metastasis, and therapy resistance. Its dual roles in immune modulation present both challenges and opportunities. Future research should develop highly selective inhibitors of KDM5A, understand the determinants of its oncogenic or tumor-suppressive effects in specific environments, utilize advanced spatial omics techniques to clarify its exact role in the tumor microenvironment, and verify its clinical effectiveness as a biomarker and therapeutic target in human clinical trials or translating KDM5A biology into effective personalized cancer therapies.

Key words: histone lysine demethylase (KDM) 5A; tumor; tumor proliferation; tumor immunotherapy

表观遗传学主要研究基因表达的可遗传性变化。这些变化不依赖于DNA序列的改变，而是通过化学修饰如组蛋白修饰、DNA甲基化等影响基因表达，近年来发现非编码RNA和RNA修饰也是重要的表观遗传学机制[1,2]。组蛋白可以接受各种修饰，包括甲基化、乙酰化、磷酸化等，这些修饰对于基因表达的影响各不相同。其中组蛋白甲基化修饰主要发生在组蛋白H3和H4的赖氨酸或精氨酸残基上(H3K4、H3K36、H3K9、H4K20等)，组蛋白甲基化会使邻近基因转录增强或抑制，进而产生可遗传的基因表达变化。其中H3K4可以被单甲基化、双甲基化和三甲基化(H3K4me/me2/me3)，这些修饰广泛参与了各种生命活动的调节[3,4]。

组蛋白赖氨酸甲基化水平主要由赖氨酸甲基转移酶(lysine methyltransferases，KMTs)和赖氨酸去甲基化酶(lysine demethylases，KDMs)共同调控。KMTs可分为SET(suppressor of variegation，Enhancer of zeste，Trithorax)结构域型和非SET结构域型两大类[5]。KDMs可分为两类[6]，一类是依赖黄素腺嘌呤二核苷酸(flavin adenine dinucleotide，FAD)的胺氧化酶，包含赖氨酸特异性去甲基化酶1(lysine specific demethylase 1，LSD1)和赖氨酸特异性去甲基化酶2(LSD2)。LSD1是首个被发现的组蛋白去甲基化酶，主要催化H3K4me1/me2去甲基化。第二类为含Jumonji 结构域的去甲基化酶，属于JMJD(Jumonji domain-containing protein)家族，包含21种含有Jumonji结构域的蛋白质，能够催化组蛋白赖氨酸和精氨酸去甲基化。含Jumonji结构域的去甲基化酶分为两类，一类仅含JmjC(Jumonji C)结构域，另一类则同时含有JmjC和JmjN(Jumonji N)结构域，后者以O_2、Fe^{2+}和α-酮戊二酸(2-OG)作为辅因子，催化赖氨酸残基的去甲基化，能够有效去除 H3K4me2/me3等甲基化标记。

JMJD家族成员大都具有高度保守的JmjC和JmjN结构域，N端JmjN结构域与染色质重塑复合物的组装相关，C端JmjC结构域则构成催化核心[7]。基于其结构特征，该家族也被称为JHDM(JmjC-domain-containing histone demethylase)家族[8]。JHDM家族包含KDM2~7等6个亚家族，具有核酸结合、蛋白质与蛋白质相互作用、染色质阅读域或其他功能模体等功能域的结构[9]。其中KDM5亚家族成员包含KDM5A~5D，可以调节细胞增殖、干细胞自我更新和分化，在基因表达调控网络以及疾病发展中扮演关键角色[10]。

近来研究显示KDM5A在多种恶性肿瘤中异常表达，比如卵巢癌[11]、乳腺癌[12]、肝癌等，并和肿瘤的发生、发展、治疗和预后密切相关。本文综述了近年来关于KDM5A在肿瘤进展中的分子调控机制、介导肿瘤耐药性以及影响肿瘤免疫治疗应答的相关研究进展，为临床肿瘤的诊疗和科学研究提供参考。

1 KDM5A的结构和作用机制

KDM5A(lysine-specific demethylase 5A)也被称为含Jumonji/ARID结构域蛋白1A(JARID1A)或视网膜母细胞瘤结合蛋白2(retinoblastoma binding protein 2，RBP2)。KDM5A最初被归类到视网膜母细胞瘤蛋白(retinoblastoma protein，RB)口袋结构域结合蛋白亚家族[13]，属于依赖Fe^{2+}/2-OG含JmjC结构域的氧合酶，其去甲基化酶活性于2007年首次被发现[14]，可以特异性去除H3K4me2/me3修饰[15]。KDM5A基因位于人12号染色体，属于KDM5家族，家族成员均含有JmjN结构域、JmjC结构域、ARID结合结构域、C_5HC_2 锌指结构域以及PHD结构域等[16](如图1 d[17])。尽管编码KDM5A与KDM5B的基因位于常染色体，其蛋白产物均包含PHD3结构域、序列高度同源，且均作用于H3K4me1/2/3这一表观遗传标记，但二者调控的具体靶基因有所不同。KDM5C/D基因则分别位于X和Y染色体上，仅包含

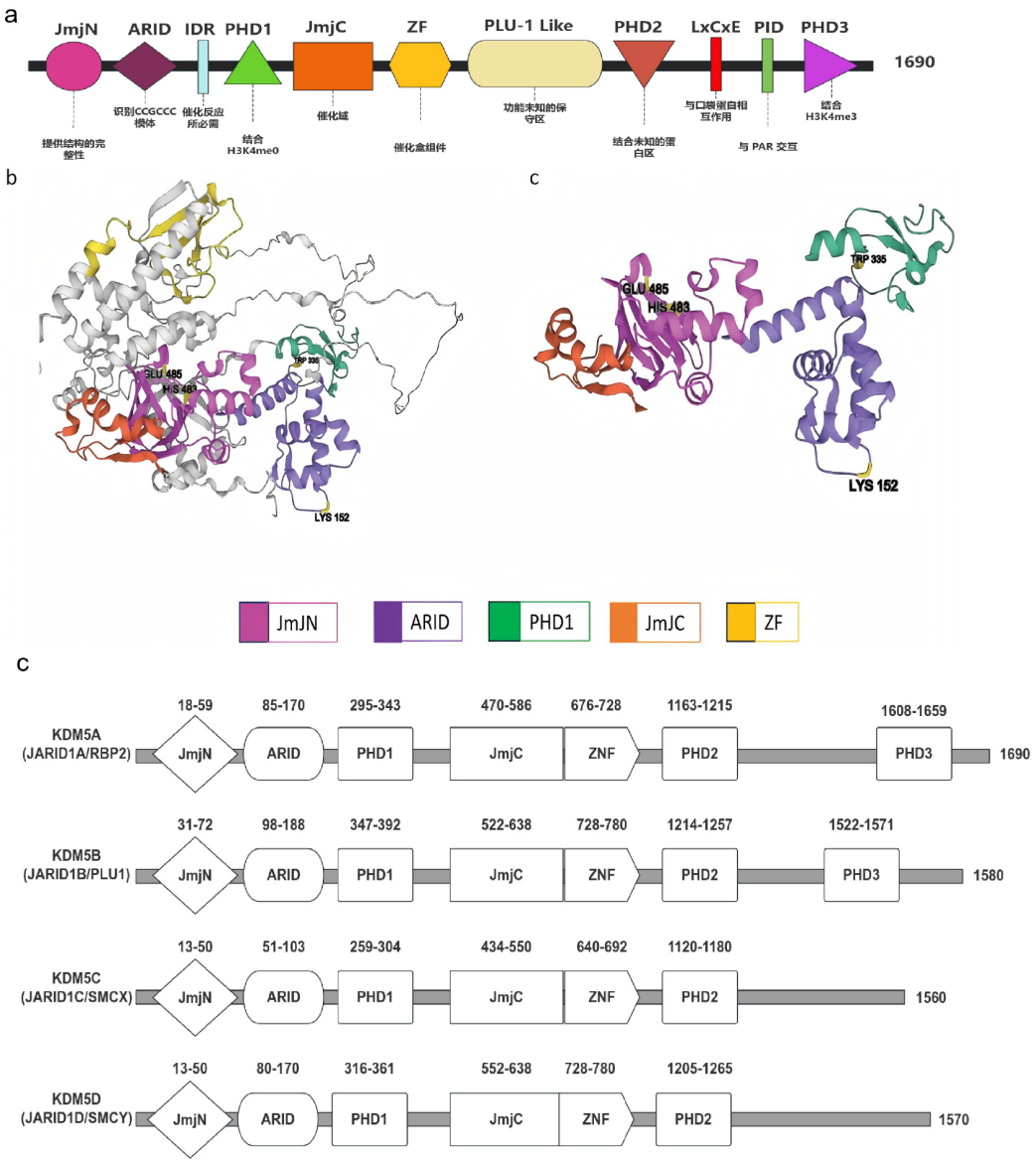

图1 KDM5A的结构[17]

a：KDM5A的结构及其功能；b：KDM5A的空间构象，突出显示了不同结构域的关键氨基酸残基（JmjC：HIS483，GLU485；ARID：LYS152；PHD1：TRP335）；c：KDM5A不同结构域的空间构象，该图只显示了关键结构域；d：KDM5家族成员结构图。

Figure 1 Structure of KDM5A[17]

a: The structure and functions of each part of KDM5A; b: Spatial conformation of KDM5A, highlighting the key amino acid residues in different domains (JmjC: HIS483, GLU485; ARID: LYS152; PHD1: TRP335); c: Spatial conformation of different domains of KDM5A, only showing the key domains in this figure; d: Structure diagram of KDM5 family members.

PHD1和PHD2结构域，具有相同的生物学功能，能去除H3K4me2/3修饰；KDM5A/B通常抑制转录，KDM5C/D则相反；KDM5A/B通常是致癌的，而KDM5C/D则发挥抑瘤作用。

KDM5A N端的JmjN与转录相关；AT-Rich相互作用结构域（A-T rich interaction domain，ARID）可与DNA尾部的CCGCCC尾部结合，增强其锚定能力[10]。内在无序区域（intrinsically disordered region，IDR）包含双功能精氨酸富集基序，能结合H2A/H2B酸性区域和核小体DNA，是KDM5A 催化反应所必需的[18]；PHD1可增强KDM5A催化活性；JmjC负责催化H3K4me2/me3的去甲基化；C_5HC_2锌指结构专一性识别H3R2和H3Q5，进而提高H3K4me3的底物专一性；PLU-1结构域的功能尚未确定；PHD2可识别结合H3K4me2，其缺失会破坏蛋白质空间结构；LxCxE（leucine-x-cysteine-x-glutamic acid motif）基

序负责KDM5A与各种口袋蛋白的相互作用,KDM5B中不存在该基序;聚ADP 核糖相互作用结构域(poly ADP ribose interacting domain,PID)招募KDM5A 到复制叉上的DNA损伤位点[19];PHD3能特异性识别并结合H3K4me3,将KDM5A招募到染色质上(图1a)。

KDM5A以Fe^{2+}和2-OG作为辅因子执行H3K4去甲基化修饰功能。它首先特异性识别三甲基化修饰的赖氨酸(H3K4me3),在氧气参与下,借助Fe^{2+}和2-OG的催化作用,使组蛋白上的甲基化赖氨酸转化为不稳定的羟基化中间体,同时生成琥珀酸与 CO_2。该中间体进一步水解,最终产生二甲基化赖氨酸(H3K4me2)和甲醛[20]。完成这一步后,KDM5A 再以相同的催化机制,继续对 H3K4me2 进行去甲基化修饰。随后以相同方式催化H3K4me2的去甲基化过程。KDM5A可通过ARID和PHD被直接募集到染色质;或与口袋蛋白、转录因子以及染色质重塑因子等相互作用被招募至染色质。总之,KDM5A的表达受到多个信号通路交叉作用,通过去除H3K4me3修饰,影响染色质构象,从而抑制邻近基因的转录,进而调节细胞的各项生命活动[21]。

2 KDM5A的生物学功能和表达调控

近年来研究证实KDM5A在细胞周期、细胞分化、细胞凋亡和昼夜节律中发挥重要调控作用,并受多种上游信号通路调控。

KDM5A参与调控细胞周期进程。在生理条件下,KDM5A可抑制细胞周期基因的表达,导致细胞周期停滞。E2F转录因子4(E2F transcription factor 4,E2F4)与p130形成DREAM(dimerization partner,RB-like,E2F,and multi-vulval class B)复合物,抑制细胞G_1/S 期转化,导致细胞周期停滞[22]。KDM5A ChIP-seq显示,在小鼠胚胎干细胞(mouse embryonic stem cells,mESCs)分化过程中,KDM5A与 DREAM复合物中的 E2F4存在共定位。在组织型纤溶酶原激活剂(tissue plasminogen activator,TPA)诱导 U937细胞分化中,KDM5A与E2F4共同结合到增殖细胞核抗原(proliferating cell nuclear antigen,PCNA)和核纤丝相关蛋白1(nucleolar and spindle associated protein 1,NUSAP1)等细胞周期相关基因的启动子处,抑制这些基因的表达,并产生累积效应[23]。同时研究发现,肿瘤细胞等异常分化细胞中的KDM5A可激活细胞周期基因的表达。胃癌细胞中的KDM5A mRNA和蛋白质水平都显著升高,在胃癌细胞系(AGS、BGC-823、HGC-27、KATO-Ⅲ)与宫颈癌(HeLa、SiHa)细胞中敲低KDM5A导致细胞周期蛋白依赖性激酶抑制剂(cyclin-dependent kinase inhibitors,CDKIs)基因(p21CIP1、p27kip1、p16ink4a)启动子区域 H3K4me3水平增高,基因转录增强,细胞周期停滞,衰老相关β-半乳糖苷酶(senescence-associated-beta-galactosidase,SA-β-gal)阳性细胞数量增加。用p21CIP1 siRNA和p27kip1 siRNA处理后,细胞衰老和周期停滞得到缓解[24]。另一研究使用 KDM5A抑制剂得出了类似的结论,KDM5A抑制剂 PBIT抑制了人前列腺癌细胞(RWPE-1、C4-2B、PC-3)的增殖,导致细胞周期停滞,另外SA-β-gal 染色显示KDM5A下调促进了细胞的衰老[25]。综上,KDM5A可作为细胞周期基因激活因子与抑制因子,其对于细胞周期的双重调控机制可能与微环境信号通路交叉调控有关,具体机制还有待后续研究阐明。

KDM5A同样在细胞分化中发挥促进/抑制双向功能。在小鼠3T3-L1前脂肪细胞分化模型中发现,KDM5A通过去除Wnt启动子的H3K4me3修饰,抑制Wnt表达和下游β-catenin通路活性,进而促进前脂肪细胞分化[26]。另一项研究则表明KDM5A可激活神经元分化相关基因的表达。抗霉素A和FCCP(氧化磷酸化解偶联剂)处理引起小鼠神经祖细胞线粒体的功能障碍,导致KDM5A降解,从而上调H3K4甲基化水平,干扰神经元分化关键基因如脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)和肌细胞增强因子2A(myocyte enhancer factor 2A,MEF2A)的转录,最终抑制神经祖细胞向神经元分化。这证明KDM5A表达有助于神经祖细胞的分化[27]。$PM_{2.5}$(particulate matter 2.5)暴露导致后代小鼠海马体发育受阻。研究发现KDM5A可结合在早期生长反应因子1(early growth response factor 1,EGR1)富含 H3K4me3的启动子处,$PM_{2.5}$ 处理导致 KDM5A下调,EGR1启动子 H3K4me3水平增高,其转录上调,进而下调Shh(sonic hedgehog)信号通路,抑制海马体突触的发育[28]。同时有报道称KDM5A也可抑制细胞分化。在卵巢切除(ovariectomized,OVX)小鼠模型中,骨形态发生蛋白2(bone morphogenetic protein 2,BMP2)诱导的间充质干细胞(mesenchymal stem cells,MSCs)的成骨分化受到抑制,研究发现KDM5A结合Runt相关转录因子2(runt-related transcription factor 2,

RUNX2)并富集在H3K4me3的启动子处,通过下调H3K4me3水平,抑制其转录,进而抑制成骨分化。使用KDM5A抑制剂可缓解骨质疏松期间的骨质流失[29]。后续实验进一步证实,激素性股骨头坏死(steroid-induced osteonecrosis of the femoral head,SONFH)患者骨髓间充质干细胞(bone marrow mesenchymal stem cells,BMSCs)中KDM5A水平升高,抑制 KDM5A可上调 RUNX2、骨钙素(osteocalcin,OCN)和骨桥蛋白(osteopontin,OPN)启动子处的H3K4me3 水平,促进基因表达和BMSC的成骨分化。相反,在SONFH患者中 KDM5A 高表达则抑制BMSC 成骨分化[21]。El 等[30]发现KDM5A在小鼠海马细胞中广泛表达,敲除KDM5A后小鼠海马神经元的分化加快。免疫组化分析显示,敲除KDM5A的小鼠CA1神经元比例增加而浅层神经元减少,证实KDM5A抑制海马神经元的分化。综上,KDM5A对细胞分化的双重调节作用可能源于微环境信号通路交叉调控。如 KDM5A的表达可抑制Wnt/β-catenin通路在脂肪分化中的抑制作用,促进前脂肪细胞分化;同时也能抑制Wnt/β-catenin通路抑制因子RUNX2的表达[21],进而抑制该通路对成骨分化的促进作用。

KDM5A具有抑制细胞凋亡的作用。当神经母细胞瘤细胞系(NB-1691、SK-N-SH、BE2)发生DNA 损伤时,KDM5A离开p53基因的启动子,导致 H3K4me3水平升高,p53表达上调并激活下游的凋亡信号[31]。在多囊卵巢综合征(polycystic ovary syndrome,PCOS)大鼠模型中,卵泡液来源的外泌体(follicular fluid-related extracellular vesicles,FF-Evs)中的LINC00092与KDM5A结合,催化磷酸酶和张力蛋白同源物(phosphatase and tensin homolog,PTEN)启动子H3K4me3的去甲基化,抑制了PTEN的转录和卵巢细胞的凋亡,缓解了PCOS的症状[32]。另外在子宫内膜样腺癌中,KDM5A还可通过促进细胞凋亡发挥抑瘤作用[33],其调控细胞凋亡的具体机制还待后续研究阐明。

KDM5A还能以非去甲基化酶活性在昼夜节律中发挥调节作用。小鼠肝脏中KDM5A可与CLOCK-BMAL1相互作用,通过抑制组蛋白去乙酰化酶1(histone deacetylase 1,HDAC1),增加周期昼夜节律调节因子2(period circadian regulator 2,Per2)启动子处的H3K9乙酰化来增强CLOCK-BMAL1介导的转录,促进经典昼夜节律基因的表达,进而延长昼夜节律周期[34]。

KDM5A的表达受多个上游信号通路的调控。Yan等[35]发现肝癌细胞系(HepG2、Hep3B、Huh7、SNU475、SMMC7721)中叉头框P2蛋白(forkhead box P2,FOXP2)可下调KDM5A,导致糖异生途径果糖-1,6-二磷酸酶1(fructose 1,6-bisphosphatase 1,FBP1)转录增强,糖酵解活性减弱[35]。Li等[12]发现在三阴性乳腺癌(triple-negative breast cancer,TNBC)细胞系(MDA-MB-231、Hs578T)中,F-箱蛋白22(F-box protein 22,Fbxo22)通过泛素化下调KDM5A进而增强p16的表达和DNA损伤,从而抑制TNBC 的发生与转移[12]。在人卵巢癌细胞系HCT116中,miR-421可靶向调控KDM5A抑制卵巢癌细胞的增殖[36]。在结肠癌中,LncRNA NEAT1可与E2F转录因子1(E2F transcription factor 1,E2F1)结合,抑制KDM5A表达[37]。KDM5A的表达也可被上调。在人胰腺癌HPAC和Panc1细胞系中,NADPH氧化酶4(NADPH oxidase 4,NOX4)可促进KDM5A /蜗牛家族转录抑制因子1(snail family transcriptional repressor 1,SNAIL1)途径,进而促进血管生成相关基因的表达[38]。

3 KDM5A在肿瘤中的作用

3.1 KDM5A调控肿瘤进展的分子机制

KDM5A 在多种肿瘤(前列腺癌、卵巢癌、宫颈癌[39])中表达失调,其作用具有双重性。KDM5A可通过多种方式下调靶基因启动子处的 H3K4me3水平以抑制其基因表达,直接或间接促进肿瘤的发生、发展与转移,且其表达水平可作为评估肿瘤进展及预后的重要指标;然而,亦有少数研究报道KDM5A具有抑癌功能。本文整理了部分体内外实验结论,部分已阐明的KDM5A调控机制见图2。

3.1.1 KDM5A调控PI3K/AKT通路促进肿瘤细胞增殖和迁移

磷脂酰肌醇3-激酶(phosphoinositide 3-kinase,PI3K)/蛋白激酶B(protein kinase B/AKT)通路受多步骤严格控制:PI3K活化后, PKB/AKT与质膜上的磷脂酰肌醇-3,4,5-三磷酸(PIP3)结合,并通过3-磷酸肌醇依赖性激酶1(3-phosphoinositide-dependent kinase 1,PDK1)激活后续通路[40]。研究表明PI3K/AKT信号通路在多种癌症中异常激活,从而促进肿瘤的发生和发展。

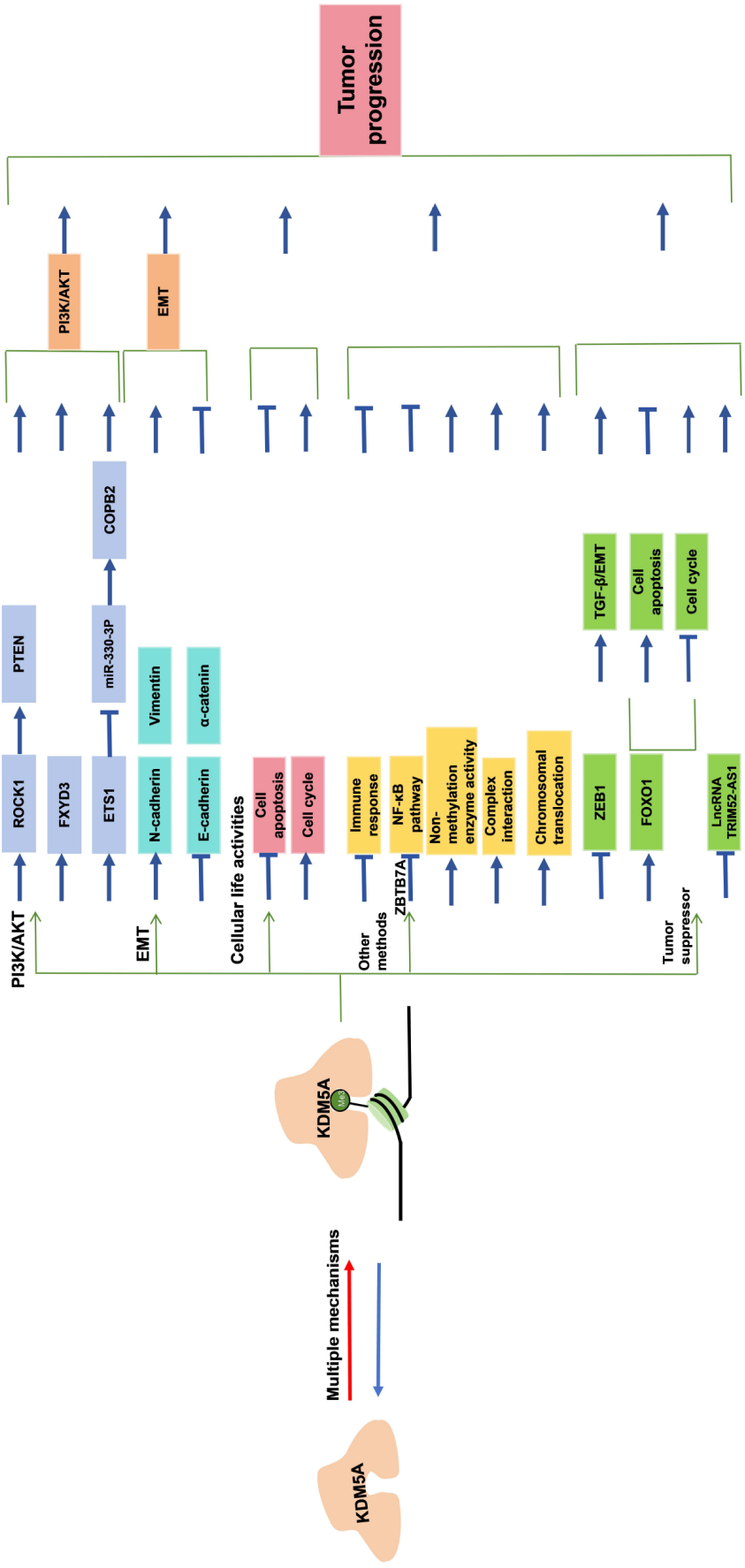

图2 KDM5A调控肿瘤发展的分子机制

Figure 2 The molecular mechanism by which KDM5A regulates tumor development

研究发现KDM5A可调控Rho激酶1（Rho-kinase 1，ROCK1）、PTEN、含FXYD结构域的离子转运调节因子3（FXYD3）、膜蛋白复合物β2亚基（coatomer protein complex subunit β 2，COPB2）等PI3K/AKT通路相关基因的表达[41-43]。KDM5A在肝癌中往往高表达，其在肝癌细胞系（HCCLM3、SMMC7721）中被敲低后可下调ROCK1，抑制PTEN/PI3K/AKT通路并减缓肝癌的进展。使用PTEN抑制剂SF1670或过表达ROCK1可以减轻KDM5A抑制剂CPI-455和顺铂（cisdiamamine dichloroplatinum，CDDP）联用产生的细胞毒性。CPI-455可下调KDM5A表达，抑制ROCK1/PTEN/AKT轴，从而增强肝癌细胞对CDDP的化疗敏感性[41]。Ma等[42]发现肝细胞癌（hepatocellular carcinoma，HCC）中的KDM5A、p-p85 和p-AKT高表达，而miR-433表达下调。研究发现 KDM5A结合在miR-433启动子处，下调H3K4me3水平以抑制其表达。在敲除KDM5A的HCC细胞（Hep3B、MHCC97H）中，miR-433表达显著升高，靶向下调FXYD3，通过抑制FXYD3-PI3K-AKT轴降低p-p85和p-AKT表达，最终抑制HCC的发生与新生血管生成[42]。并且KDM5A的高水平表达与HCC患者的不良预后相关，提示其可作为潜在治疗靶点[44]。此外，Mi等[43]报道KDM5A在前列腺癌细胞系（DU145、PC-3、VCaP、C4-2）中高表达，其通过下调原癌基因1（ETS proto-oncoprotein 1，ETS1）启动子处的 H3K4me2 水平增强ETS1 的表达，通过抑制miR-330-3p激活COPB2/PI3K/AKT轴，最终促进前列腺癌的发生与迁移。同时，KDM5A的高表达同样与前列腺癌患者的不良预后有关[43]。该研究表明KDM5A下调H3K4me2水平从而使靶基因转录增强，可能是多种调控机制交叉作用所导致。

3.1.2 KDM5A调控EMT促进肿瘤细胞侵袭与转移

上皮间充质转化（epithelial-mesenchymal transition，EMT）指上皮细胞转分化为间充质细胞的生物学过程。肿瘤细胞发生EMT时，细胞黏附能力下降，并获得间充质细胞表型，得以从原部位脱离，向周围组织和器官转移和扩散[45]。

已有研究证实，KDM5A的异常高表达能够通过特定信号通路，对上皮间质转化（EMT）过程中的关键标志物——包括N-cadherin、vimentin、E-cadherin及α-catenin等的表达进行精准调控，进而影响细胞的迁移、侵袭等生物学行为[46,47]。在人肺腺癌细胞系（SK-LI-1、Calu 3、A549）中，KDM5A的高表达促进了N-钙黏蛋白（N-cadherin）、波形蛋白（vimentin）的表达，同时下调E-钙黏蛋白（E-cadherin）、α-连环蛋白（α-catenin）的表达，进而驱动EMT进程。细胞迁移与伤口愈合实验证明，敲低KDM5A显著降低了紫杉醇耐药细胞系 PTX-Calu-3的迁移能力[46]。此外，女性常见的肿瘤中的 KDM5A 高表达也会促进 EMT 进程。Feng等[47]发现，在卵巢癌细胞系（SKOV3、OVCA429、SKOV3/PTX）中，KDM5A呈现高表达并促进 EMT 进程。KDM5A在SKOV3细胞中过表达可上调N-cadherin，并伴随E-cadherin的下调，从而促进EMT 进程，增强了肿瘤细胞的侵袭和转移能力。

3.1.3 KDM5A 调控细胞周期与凋亡

KDM5A可以下调细胞周期抑制基因和促凋亡基因的表达，促进肿瘤细胞增殖。研究表明KDM5A可调控Bax、Bcl-2、p27、P21等与细胞周期和凋亡相关基因的表达[48,49]。Wu 等[48]发现肺腺癌组织中KDM5A表达显著升高，在肺腺癌细胞系SK-LU-1中使用RNAi敲低KDM5A导致Bax上调和Bcl-2下调，从而促进细胞凋亡并抑制细胞增殖。同时，敲低KDM5A显著提高了肺腺癌细胞系SK-LU-1对吉非替尼的敏感性，提示KDM5A可能作为肺腺癌治疗的潜在靶点[48]。Peng等[49]研究发现，KDM5A在骨肉瘤组织中的表达显著高于正常组织，CRISPR/Cas9技术敲除KDM5A后，骨肉瘤细胞（MG-63、143B）发生周期停滞。RT-qPCR显示，KDM5A敲除后细胞周期依赖性激酶抑制剂1B（cyclin dependent kinase inhibitor 1B，CDKN1B）和细胞周期蛋白D1（cyclin dependent protein 1，Cyclin D1）下调，并伴随p27、P21和Bax上调，从而抑制细胞周期、促进细胞凋亡，最终抑制骨肉瘤细胞的增殖。转录组分析显示KDM5A通过激活与细胞生长相关的多个信号通路参与骨肉瘤的增殖。

3.1.4 KDM5A 通过其他途径参与肿瘤进程

KDM5A可以调控免疫相关基因。Liu等[50]发现KDM5A在上皮性卵巢癌ID8小鼠肿瘤模型中下调抗原加工和呈递途径基因（下调HLA-A和HLA-B），抑制效应$CD8^+$ T细胞的免疫反应，从而促进肿瘤发生。在部分乳腺癌中KDM5A发生基因扩增，乳腺癌细胞系SUM149和SUM149CR中的KDM5A和含锌指和BTB结构域7A（zinc finger and BTB

domain containing 7A,ZBTB7A)共同结合在靶基因启动子处,下调H3K4me3水平,导致NF-κB信号通路和线粒体相关通路基因表达下调,从而促进了乳腺癌细胞的增殖[51]。该研究中观察到的NF-κB通路抑制作用可能与特定微环境下的信号通路交叉调控有关。

KDM5A也能与蛋白质复合体相互作用促进肿瘤增殖。在宫颈癌细胞HeLa和乳腺癌细胞系MCF7中,KDM5A与含GATA锌指结构域1(GATA zinc finger domain containing 1,GATAD1)、EMSY及Sin3/HDAC复合体相互作用,促进肿瘤细胞增殖。值得注意的是,尽管该复合体的各组分(KDM5A、EMSY及HDACs)通常与转录抑制功能相关,但在该特定过程中,它们协同发挥正向调控作用[52]。进一步发现在HeLa、MCF7细胞中,只有具有完整JmjC和JmjN结构域的KDM5A才能同时与SIN3B和NuRD复合体物理结合,并且KDM5A通过NuRD(nucleosome remodeling and deacetylase)复合体间接与含锌指结构的MYND型蛋白8(zinc finger MYND-type containing 8,ZMYND8)相互作用,协同调节 H3K4m2/3 的水平,从而调控肿瘤的发展[53]。在人乳腺癌细胞(MDA-MB-231、LM2)中,KDM5A以不依赖去甲基化酶的方式激活乳腺癌中的肌腱蛋白C(tenascin C,TNC)表达,从而促进乳腺癌的转移,敲低KDM5A可抑制乳腺癌细胞的肺部转移[54]。

KDM5A还可通过染色体易位形成致病融合蛋白(如 NUP98-KDM5A)参与肿瘤发生。这一现象于2006年被首次发现[55],在儿童白血病中具有较高比例[56,57],其作用机制也具有代表性:核孔蛋白98和96前体蛋白(nucleoporin 98 and 96 precursor,NUP98)-KDM5A融合蛋白通过其PHD3结构域识别急性髓样白血病(acute myeloid leukemia,AML)相关基因启动子处富集的H3K4me3,通过多种机制激活基因转录,最终促进AML的发生[58]。一项研究构建了AML细胞系iPSC-NK5A,其可以表达 NUP98-KDM5A融合蛋白,机制研究发现NUP98-KDM5A 复合物通过 PHD3 结构域识别并结合 AML 相关基因启动子处的H3K4me3,促进DNA损伤和磷酸化的组蛋白H2AX(phosphorylated histone H2AX,γ-H2AX)积累;或通过与核糖核酸输出蛋白1(ribonucleic acid export 1,RAE1)相互作用干扰RAE1活性,导致有丝分裂发生错误。上述机制共同导致染色质不稳定并促进 AML 的进展[59]。近期研究显示,Janus激酶/信号转导及转录激活因子(Janus kinase/signal transducers and activators of transcription,JAK-STAT)信号通路基因以及细胞周期蛋白依赖性激酶6(cyclin dependent kinase 6,CDK6)是NUP98-KDM5A的下游靶点,并且NUP98-KDM5A 引发的 AML 对 JAK 或 CDK6的抑制较为敏感[60,61]。

3.1.5 KDM5A抑制肿瘤细胞增殖

大部分研究表明KDM5A是典型的促癌因子,但近期报道KDM5A在肿瘤中还可行使抑癌作用。

KDM5A与叉头框蛋白O1(forkhead box O1,FOXO1)在子宫内膜样腺癌中下调,研究发现KDM5A可促进FOXO1去乙酰化,加强与DNA的结合能力,进而抑制细胞周期进程和细胞增殖,并促进肿瘤细胞凋亡[33]。Dai等[62]发现与原发性胶质瘤相比,转移性胶质瘤中的KDM5A水平较低。研究发现神经胶质瘤系(SW1783、LN-229)中KDM5A 通过下调锌指E环结合同源框1(zinc finger E-box binding homeobox 1,ZEB1)处的H3K4me3水平,抑制ZEB1转录,通过ZEB1/TGF-β/EMT轴,抑制神经胶质瘤的迁移与侵袭,并且KDM5A的低水平与患者的不良预后程度有关。此外,KDM5A在AML患者中常高表达并伴随 LncRNA TRIM52-AS1表达下调,敲低AML细胞HL-60中KDM5A可减少其在TRIM52-AS1的上游启动子处的富集,上调 H3K4me3 的水平并促进TRIM52-AS1的表达,进而促进细胞增殖与迁移。因此,KDM5A可抑制TRIM52-AS1进而抑制AML细胞增殖与迁移,该研究为AML治疗提供了潜在靶点[63]。

KDM5A具备的促癌、抑癌作用,均依赖于对靶基因启动子处H3K4me3进行去甲基化,对功能差异的靶基因转录进行抑制,从而发挥不同功能。发挥促癌作用时,KDM5A主要沉默抑癌基因,如 PTEN[41]、HLA-A/B[50]或上皮维持基因E-cadherin[46,47];发挥抑癌作用时,KDM5A抑制促癌基因如ZEB1[62]或与转录因子FOXO1协同[33],抑制肿瘤的迁移与增殖。其次,缺氧、炎症等肿瘤微环境也可能重塑KDM5A的基因组定位,如在人胰腺癌HPAC和Panc1细胞系中,在缺氧条件下通过缺氧诱导因子1α(hypoxia-inducible factor 1-alpha,HIF-1α)招募KDM5A至Snail启动子处[38]或通过组织特异性转录因子如胶质瘤中的FOXO1可能决定KDM5A的靶向偏好性[33]。综上,

KDM5A发挥促癌或抑癌作用具有肿瘤类型依赖性,可为癌症的治疗方案提供参考。

3.2 KDM5A与肿瘤耐药

KDM5A与肿瘤耐药关系密切。有报道称KDM5A参与耐药肿瘤细胞(drug-tolerant persister cells,DTPs)的形成,在表皮生长因子受体(epidermal growth factor receptor,EGFR)突变型非小细胞肺癌衍生细胞系 PC9中,敲低KDM5A并未影响增殖,但在联合使用酪氨酸激酶抑制剂(tyrosine kinase inhibitors,TKIs)后,DTPs的数量显著减少,说明KDM5A参与建立耐药性所需染色质不稳定状态。机制研究发现胰岛素样生长因子1受体(insulin-like growth factor 1 receptor,IGF1R)通过 KDM5A参与耐药,敲低IGF1R导致KDM5A表达下调,进而抑制 PC9细胞的药物耐受性[64]。

KDM5A通过表观遗传学修饰调控多种药物的耐药性,其表达在厄洛替尼和紫杉醇耐药性的发展过程中显著升高[65]。Xu等[46]发现紫杉醇耐药的PTX-Calu-3细胞中KDM5A表达显著上调。在耐药PTX-Calu-3细胞中过表达KDM5A可增加P-糖蛋白(P-glycoprotein,P-gp)的表达,而P-gp表达升高与耐药性相关。在另一项研究中,敲低KDM5A后,SK-LU-1肺腺癌细胞对吉非替尼的敏感性显著提高[48]。在胰腺导管腺癌(pancreatic ductal adenocarcinoma,PDAC)中KDM5A的表达与耐药相关,吉西他滨耐药细胞中KDM5A/C的表达显著升高,研究显示KDM5A/C可作为CD44的下游分子促进吉西他滨耐药[66]。在他莫昔芬耐药的雌激素受体(estrogen receptor,ER)(+)乳腺肿瘤中,KDM5A能激活IGF1R和ErbB信号通路,导致PI3K/AKT/mTOR通路的激活和他莫昔芬耐药的发生[67]。此外,抑制KDM5A 能够增强WEE1抑制剂AZD1775抑制耐药性AML细胞增殖的能力[68]。

综上,KDM5A在肿瘤中通过多种表观遗传调控机制促进肿瘤细胞耐药性。然而,部分耐药机制并非完全依赖其表观遗传学修饰功能,如KDM5A还与HDAC复合体发生物理相互作用,降低HeLa和MCF-7细胞的放射敏感性[52,69],故KDM5A介导肿瘤耐药性的具体机制仍需进一步阐明。

3.3 KDM5A 与肿瘤免疫治疗

免疫检查点阻断(immune checkpoint blockade,ICB)疗法旨在通过增强免疫系统对癌症的特异性识别和应答来治疗肿瘤。尽管ICB疗法的影响日渐增强,但因其适用人群有限,限制了广泛应用。Wang等[70]发现ICB的阻断反应与KDM5A高表达相关,并据此鉴定出同时增加KDM5A和关键免疫检查点蛋白水平的化合物D18,且在小鼠肿瘤模型中发现KDM5A的高表达显著增强程序性细胞死亡蛋白-1(programmed death-1,PD-1)的治疗效果。深入的机制研究揭示了D18调控抗肿瘤免疫的多重作用路径:首先,D18可上调KDM5A的表达,通过其去甲基化功能降低PTEN启动子区域的H3K4me3修饰水平,从而抑制PTEN的表达;其次,PTEN的下调可激活PI3K-AKT-S6K1信号通路,进而上调PD-L1的表达;与此同时,D18还能直接激活TLR7/8信号通路,促进活化$CD8^+$T细胞向肿瘤部位募集。这些效应相互协同,最终显著增强活化T细胞的增殖活性及其对肿瘤细胞的特异性杀伤能力。在另一研究中,聚ADP核糖聚合酶抑制剂(poly ADP ribose polymerase inhibitor,PARPi) Niraparib和PD-L1阻断联合治疗对宫颈癌疗效显著。研究发现Niraparib 通过上调KDM5A,从而下调PTEN启动子的 H3K4me3水平和基因转录,并经由PI3K-AKT-S6K1 通路上调了PD-L1的丰度。生物信息学分析结果表明,在小鼠宫颈癌模型中,Niraparib可显著增加$CD8^+$T免疫细胞的肿瘤浸润程度及肿瘤微环境中整体免疫细胞的丰度。这一作用不仅有助于重塑并改善肿瘤免疫微环境,还能在增强$CD8^+$T细胞活化水平的同时,提升其对肿瘤细胞的特异性杀伤能力,最终显著增强免疫检查点抑制剂(ICB)联合疗法的抗肿瘤疗效[71]。近期研究显示KDM5突变与增强的肿瘤免疫原性、免疫细胞的丰富浸润和免疫反应的改善有关[72]。综上,KDM5A的表达对ICB治疗有重要作用,但现有结论来源于小鼠移植肿瘤模型研究,尚缺乏临床验证。此外,KDM5A对免疫应答存在双重调控:一方面可下调抗原呈递途径(HLA-A/B)抑制$CD8^+$T细胞活化[50],另一方面则可能通过 PI3K-AKT-S6K1轴上调PD-L1的表达并增强$CD8^+$T的活化水平[72,73],其净效应可能取决于肿瘤免疫微环境状态。

除ICB外,目前多种靶向KDM5A的抑制剂已与免疫疗法、化疗、放疗及靶向疗法联用,以探究其抗癌效果。值得注意的是,KDM5A高表达与肿瘤患者不良预后相关,提示其作为预后标志物的潜力[43,44,62]。

表1总结了KMDM5A在不同肿瘤中的作用机制。

4 KDM5A抑制剂

鉴于ICB疗法在肿瘤免疫治疗中的潜在疗效，KDM5A抑制剂成为目前的研究热点。最早发现的一种名为CPI-455的泛KDM5抑制剂，可抑制KDM5A结合在靶基因的启动子处，但该抑制剂仍处于临床前阶段[74]。Fang等[41]发现，在异种移植肿瘤模型中，CPI-455与CDDP联合治疗可以显著抑制肿瘤的生长，且不会引起全基因组H3K4me3水平剧烈波动[74]。另外，在前列腺癌细胞(PNT1A、LNCaP、C4-2、22RV1、PC3、Du145)中，CPI-455可有效抑制 KDM5家族成员的活性，从而抑制前列腺癌侵袭与转移[75]。KDOAM-25是一种双靶点 KDM5A/5B抑制剂，本质为酰胺类化合物，对2-OG氧化酶亚家族具有高选择性，目前也处于临床前试验阶段。Tumber等[76]发现KDOAM-25能显著上调骨髓瘤细胞中H3K4me3水平。Iida等[77]发现了一类基于蛋白质水解靶向嵌合体(protein hydrolysis-targeted chimeric entity，PROTACs)的新型KDM5A抑制剂化合物20b和23b，它们可作为治疗神经退行性疾病的药物。化合物20b和23b通过PROTAC介导的蛋白酶体途径降解神经母细胞瘤神经2a细胞中的KDM5A，显著促进神经突生长，进而抑制神经退行性疾病的发生，其靶向降解策略有望克服传统抑制剂的选择性瓶颈。

广谱Jumonji抑制剂JIB-04可以针对KDM5A/B/C、KDM4A/D等多个亚型，目前处于II期临床试验阶段。早期研究发现，JIB-04不仅可以直接发挥抗肿瘤作用，还可以间接抑制耐药细胞的生长，有望改善肿瘤化疗的耐药性[78,79]。Kim等[80]发现JIB-04通过抑制Wnt/β-Catenin信号通路，从而抑制结直肠癌的侵袭和转移。Lee等[81]发现JIB-04通过靶向KDM途径抑制H3K4me去甲基化过程，导致肝癌细胞周期停滞，并抑制肿瘤干细胞特性与HCC增殖。在AML中，JIB-04抑制KDM5A的表达，并抑制mTOR通路DNA损伤诱导转录物4(DNA damage inducible transcript 4，DDIT4)的表达，从而抑制细胞增殖并诱导细胞凋亡，同时DDIT4的高表达与AML不良预后相关[73]。同时，JIB-04与维奈克拉联合使用可协同抑制AML细胞的增殖并诱导其凋亡，且该联合治疗对不同亚型的AML细胞均有效，目前已进入II期临床联合用药试验[82]。

虽然越来越多的靶向KDM5A抑制剂被发现，但目前也仅只有LSD1抑制剂GS-5801进入慢性乙型肝炎I期临床试验阶段[83]，其余的靶向抑制剂仍然在研发中。当前KDM5A抑制剂仍然面临转化瓶颈，

表1 KDM5A在不同肿瘤中的作用

Table 1 The role of KDM5A in different tumors

类型	KDM5A表达	相关因子	作用	参考文献
肝癌	↑	ROCK1、PTEN、AKT	促进细胞增殖、迁移	[41]
肝细胞癌	↑	miR-433、FXYD3、p-p85、p-AKT	促进血管生成和细胞增殖	[42]
前列腺癌	↑	miR-330-3p、COPB2/PI3K/AKT	促进细胞侵袭、增殖	[43]
肺腺癌	↑	N-cadherin、vimentin、E-cadherin、α-catenin	促进细胞侵袭、迁移	[46]
卵巢癌	↑	N-cadherin、E-cadherin	促进细胞侵袭、迁移	[47]
肺腺癌	↑	Bax、Bcl-2	抑制细胞凋亡，促进细胞增殖	[48]
骨肉瘤	↑	CDKN1B、Cyclin D1、p27、P21、Bax	促进细胞增殖，抑制细胞凋亡	[49]
上皮性卵巢癌	↑	HLA-A、HLA-B	抑制免疫反应，促进癌症发生	[50]
乳腺癌	↑	ZBTB7A、NF-κB	促进细胞增殖	[51]
宫颈癌	↑	GATAD1、EMSY、Sin3/HDAC复合体	促进细胞增殖	[52]
乳腺癌	↑	NuRD复合体、ZMYND8	促进肿瘤发生	[53]
乳腺癌	↑	TNC	促进细胞侵袭、转移	[54]
白血病	形成NUP98-KDM5A	RAE1、γ-H2AX	促进肿瘤发生	[59]
子宫内膜样腺癌	↓	FOXO1	抑制细胞增殖，促进细胞凋亡	[33]
神经胶质瘤	↓	ZEB1	抑制细胞侵袭和转移	[62]
白血病	↑	LncRNA TRIM52-AS1	促进细胞增殖与迁移	[63]

注：“↑”表示KDM5A表达上调，“↓”表示KDM5A表达下调。

Note: ″↑″ indicates that the expression of KDM5A is upregulated, while ″↓″ indicates that the expression of KDM5A is downregulated.

如KDM5A与KDM5B/C结构高度相似,加大了开发靶向抑制剂的难度;部分靶向抑制剂如PROTAC类降解剂在中枢神经系统肿瘤中效果不佳,仅抑制KDM5A的表达可能不足以降低靶基因的表达;最后,存在肿瘤耐药机制,从而削弱靶向KDM5A抑制剂的疗效。

5 研究展望

KDM5A广泛参与恶性肿瘤的发生、发展和预后过程。KDM5A通过抑制抑癌基因的表达,维持肿瘤干细胞的特性;通过与相关信号通路交叉作用,驱动细胞增殖、迁移和耐药;通过微环境重塑作用,在缺氧环境下促进血管新生,促进肿瘤适应性生长,并且KDM5A的表达与多种肿瘤的不良预后相关。因此,KDM5A在临床上是颇具潜力的药物靶点,但仅有少数的抑制剂被证实在临床上有一定的特异性,其毒性及耐药机制仍需深入探索。目前该领域临床前研究多采用小鼠模型或有限的细胞系模型,这类模型难以全面复现肿瘤的分子异质性特征。且临床相关性依赖于肿瘤基因组图谱的数据,难以代表人群差异。与KDM抑制剂相关的研究大多采用单层培养,忽略了肿瘤微环境的影响。针对KDM的靶向抑制剂的底物选择性和脱靶效应,需要结合结构生物学和人工智能来设计。借助单细胞测序与空间转录组技术,能够系统解析KDM5A在肿瘤不同区域及细胞亚群中的动态调控作用,为深入阐释肿瘤微环境的复杂构成及时空异质性特征提供关键技术手段与研究视角。PROTAC技术可使KDM5A抑制剂靶向性更强,但其在不同系统的抑制效率不同,仍需完善。寻找高选择性的KDM5A抑制剂,可为恶性肿瘤的个性化治疗提供分子基础,并且靶向KDM5A抑制剂在帮助恶性肿瘤克服化疗耐药性方面也有着广泛的应用前景。

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